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L12	L11 same l8	0	L12
L11	L10 with l9	3	L11
L10	HMPAO	86	L10
L9	glutathione	23359	L9
L8	L7 with l6	184	L8
L7	conjugated or complexed or bound	478694	L7
L6	L5 with (l3 or l1)	765	L6
L5	l4 or l2	1804556	L5
L4	colloid	85710	L4
L3	ligand with anti-ligand	990	L3
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L13: Entry 1 of 1 File: PGPB Nov 7, 2002

PGPUB-DOCUMENT-NUMBER: 20020164648
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020164648 A1

TITLE: Methods and compositions for delivery and retention of active agents to lymph nodes

PUBLICATION-DATE: November 7, 2002

US-CL-CURRENT: 435/7.1

APPL-NO: 10/ 044650 [PALM]
DATE FILED: January 14, 2002

RELATED-US-APPL-DATA:
Application 10/044650 is a continuation-of US application PC/T/US00/18135, filed June 30, 2000, UNKNOWN
Application is a non-provisional-of-provisional application 60/143742, filed July 14, 1999,

L11: Entry 2 of 3 File: USPT Feb 11, 1997

DOCUMENT-IDENTIFIER: US 5601800 A
TITLE: New multifunctional ligands for potential use in the design therapeutic or diagnostic radiopharmaceutical imaging agents

Other Reference Publication (36):
Suess et al., ".sup.99m Tc-d, 1-HMPAO uptake and glutathione content in brain tumors" J Nucl Med 32:1675-1681, 1991.

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L11: Entry 2 of 3 File: USPT Feb 11, 1997

DOCUMENT-IDENTIFIER: US 5601800 A
TITLE: New multifunctional ligands for potential use in the design therapeutic or diagnostic radiopharmaceutical imaging agents

Other Reference Publication (36):
Suess et al., ".sup.99m Tc-d, 1-HMPAO uptake and glutathione content in brain tumors" J Nucl Med 32:1675-1681, 1991.

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L11: Entry 3 of 3 File: USPT Sep 1, 1992

DOCUMENT-IDENTIFIER: US 5143713 A
TITLE: .sup.99m Tc labeled liposomes

Brief Summary Text (24):
After incubation, excess labeled carrier and antioxidant may be washed from the LL or LELP. Since the labeling is so efficient, only a few percent of the initial radioactivity is found in the wash. In cases where the carrier and antioxidant are relatively innocuous, the washing is optional and the labeled liposomes may be used directly after incubation. This would be the case, for example, when the antioxidant is glutathione and the carrier is HMPAO. If separation is desired, centrifugation at 10-20,000 .times.g may be used or, a rapid and convenient separation may be effected with a syringe pack column attached to the syringe containing the labeled liposomes. The liposomes will pass in the void volume while any free radionuclide, pertechnetate for example, would be retained on the column. In a most preferred labeling procedure for clinical use, a freeze dried preparation of .sup.99m Tc-HMPAO is reconstituted with .sup.99m TcO.sub.4.sup.- and immediately incubated at room temperature with liposomes or liposome-encapsulated hemoglobin for a period as short as 5 minutes prior to use in a patient. Washing is not necessary.

Detailed Description Text (6):
The discovery of an efficient labeling method for liposomes resulting in labeled liposomes that are stable in vitro and in vivo solves one of the more important problems in liposome labeling. The method is illustrated with the use of .sup.99m Tc-labeled HMPAO as a carrier to introduce the label into a preformed liposome. Glutathione, ascorbic acid or other suitable antioxidant is most preferably encapsulated within the liposome prior to incubation with a labeled carrier to achieve efficient labeling. Possibly glutathione or other reducing agents convert the .sup.99m Tc HMPAO complex into a more hydrophilic form that is retained inside the liposome (Ballinger, J. R., Reid, R. H. and Gulenchyn, K. Y., J. Nucl. Med., 29, 1998-2000(1988); Lang, J. J., J. Nucl. Med., 31, 1115 (1990); Ballinger, J., J. Nucl. Med., 31, 1115-1116 (1990)).

Detailed Description Text (16):
Liposome-encapsulated hemoglobin (prepared as described in Example 1 or purchased from Vestar, Inc., San Dimas, Calif. or Naval Research Laboratories, Washington, D.C.) was washed 3 times with phosphate buffered saline by centrifugation and resuspended with phosophate buffered saline to remove subcellular-sized debris and free hemoglobin. LEH containing glutathione or ascorbic acid was resuspended in PBS to yield a hematocrit value of approximately 50. .sup.99m Tc (10 mCi) in 5 ml sterile water for injection was used to reconstitute hexamethylenepropylene amine oxime (HMPAO) supplied as a freeze dried preparation (Ceretec.TM., Amersham, Arlington Heights, Ill.) for 5 min at room temperature. This mixture of .sup.99m Tc-HMPAO complex and glutathione was then incubated with LEH (10 mg -1000 mg total lipid dose of LEH containing 2.5-300 mg intravesicular hemoglobin) for 5 minutes with intermittent swirling after which the radio-labeled LEH was washed (centrifugation at 20,000 .times.g for 30 minutes) with PBS and the labeling efficiency determined (bound to pellet/total). LEH was then resuspended to a

constant lipid dose for injection.

Detailed Description Text (18):
The .sup.99m Tc-labeled LEH exhibited excellent in vitro stability over a period of at least 90 hours storage in lactated Ringer's solution, as shown in FIG. 3 and in FIG. 9. FIG. 3 shows the stability of liposome-encapsulated labelled hemoglobin prepared from LEH purchased from Naval Research Laboratories and incubated with .sup.99m Tc-HMPAO without the addition of glutathione (glutathione is present as a result of the particular method of preparation of LEH). FIG. 9 shows the stability of liposome-encapsulated labelled hemoglobin prepared as described above with glutathione present at a concentration of 20 mM or 100 mM.

Detailed Description Text (22):
Liposomes prepared as described in Example 1 above or purchased from a commercial source (Vestar, San Dimas, Calif.) and containing 30 mM or 100 mM glutathione were incubated with .sup.99m Tc-HMPAO. The percent of initial .sup.99m Tc associated with the liposomes was measured before and after washing and compared with the amount of label retained in liposome-encapsulated labeled hemoglobin. The results are shown in FIG. 9 and FIG. 11. There was virtually no loss of .sup.99m Tc label from liposomes or liposome-encapsulated hemoglobin prepared by incubating with .sup.99m Tc-HMPAO in the presence of glutathione. Labeling efficiency was less than 20% when glutathione was absent and there was a loss of almost 50% of the label after a single wash.

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L15: Entry 11 of 87 File: PGPB Jan 2, 2003

DOCUMENT-IDENTIFIER: US 20030003143 A1
TITLE: Lipidic microparticles linked to multiple proteins

Brief Description of Drawings Paragraph:
[0099] Immunolipid:nucleic acid complexes of the present invention may be prepared by incorporating the Fab' fragment into the liposomes or lipids by a variety of techniques well known to those of skill in the art. The Fab' is added to the lipid:nucleic acid complex either before or after complex formation. For example, a biotin conjugated Fab' may be bound to a liposome containing a streptavidin. Alternatively, the biotinylated Fab' may be conjugated to a biotin derivatized liposome by an avidin or streptavidin linker. Thus, for example, a biotinylated monoclonal antibody was biotinylated and attached to liposomes containing biotinylated phosphatidylethanolamine by means of an avidin linker (see, e.g., Ahmad et al., Cancer Res. 52: 4817-4820 (1992)). Typically about 30 to 125 and more typically about 50 to 100 Fab' fragments per lipid:nucleic acid complex are used.

Detail Description Paragraph:
[0201] 300 nmol of Mal-PEG-DSPE in 0.5 ml of chloroform were placed in a glass test-tube and the solvent was removed in vacuum. The dry residue was dissolved in 1 ml of MES-20 buffer (20 mM morpholinoethane sulfonic acid, 144 mM sodium chloride, 2 mM ethylenediamine tetraacetic acid, and NAOH to pH 6.0). 2,5 ml of solution containing 0.57 mg/ml of Fab' fragments of a recombinant humanized monoclonal antibody against extracellular domain of HER2 oncoprotein (rhuMAbHER2, Genentech, Inc.) was added to the Mal-PEG-DSPE solution, and the pH was carefully adjusted to 7.2-7.4 with diluted NaOH. The mixture was incubated under argon at room temperature for 2.5 hours, and the reaction was stopped by addition of 0.2 M cysteine hydrochloride to a final concentration of 5 mM. Fifteen minutes after the addition of cysteine, the reaction mixture was dialyzed against HEPES-buffered saline (20 mM hyrdoxyethylpiperazino ethanesulfonic acid, 144 mM NaCl, NaOH to pH 7.2), concentrated by ultrafiltration through a YM-10 membrane (Amicon) under pressure, and sterilized by filtration through a 0.2 .mu.m cellulose acetate filter. The reaction products were analyzed by polyacrylamide gel electrophoresis in the presence of sodium dodecyl sulfate (SDS-PAGE), with Coomassie Blue staining. Total protein was determined the dye binding assay (Bio-Rad). The assay revealed 62% conversion of the original protein (M.w. 46,000) into slower-moving product (M.w. 49,000) consistent with the expected conjugate. Total protein recovery in the products was 98%.

Detail Description Paragraph:
[0205] Small (100 mn) unilamellar liposomes containing entrapped pH-sensitive fluorescent indicator 8-hydroxypyrene trisulfonic acid were prepared from a mixture of 1-palmitoyl-2oleoyl-phosphatidylcholine (Avanti), cholesterol (Calbiochem), and methoxypolyoxyethyleneglycol (M.w. 1,900)-derivatized distearoyl phosphatidylethanolamine (Sygena) in the molar ratio of 30:20:3 as described by Kirpotin et al. (Biochemistry, 36:66-75 (1997)), and sterilized by filtration through 0.2 .mu.m cellulose acetate filter. 0.26 ml of liposome preparation containing 2 .mu.mol of phospholipids was mixed with 0.106 ml of a solution containing 100 .mu.g of the anti-HER2 Fab'-PEG-DSPE conjugate prepared according to Example 4, above, and incubated overnight at 37.degree. C. Following incubation, the liposomes were separated from unbound material by gel-filtration on a column

with Sepharose 4B (Pharmacia), using HEPES-buffered saline as eluent. The liposomes were eluted in the void volume of the column. The amount of liposome-bound protein was determined by the Bio-Rad dye binding assay, and the liposome concentration was measured by total phosphorus using molybdate method (Morrison, Anal. Biochem., 7:218-224 (1964). SDS-PAGE of the liposomes (see Example 13, below) revealed the presence of anti-HER2 Fab'-PEG-DSPE conjugate, but no free anti-HER2 Fab' in the liposome preparation. Liposome-associated protein was quantified by SDS-PAGE (see Example 13) and binding of the added Fab'-PEG-DSPE conjugate with the liposomes was expressed as percentage of the output protein/phospholipid ratio over the input protein/phospholipid ratio. The binding of Fab'-PEG-DSPE conjugate to the liposomes was 80%. The leakage of HPTS from the liposomes during incubation with the protein-PEG-DSPE conjugate to the liposomes was less than 2%.

Detail Description Paragraph:
[0219] The amount of protein-PEG conjugate in the conjugation product and in the liposomes was assayed by polyacrylamide gel electrophoresis in the presence of sodium dodecylsulfate (SDS-PAGE) under non-reducing conditions according to Laemmli (1974). Typically, 5-20 .mu.L aliquots of analytical sample were mixed with 6.times.sample buffer containing SDS and track dye (bromophenol blue), incubated 1 min. at 60.degree. C., and applied onto a polyacrylamide gel (dimensions 10.times.10.times.075 cm) with a concentration of 10-12%, and cross-linker content of 2.6%. The separation was effected in a vertical slab gel electrophoresis apparatus at constant current of 30 mA. The protein bands were developed by Coomassie Blue staining using conventional methods. The conjugate formed a distinct band with lower electrophoretic mobility than the original protein. For quantitation of protein, the bands were excised, and the dye was extracted into 50% aqueous dimethylforrnamide at 100.degree. C. for 30 min. The amount of extracted dye was quantified by spectrophotometry at 595 nm, and the protein amount per band was determined by comparison to a standard curve produced from the similarly processed bands of concomitantly run standard amounts of corresponding protein 9 (Fab' or scFv).

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L15: Entry 13 of 87 File: PGPB Dec 12, 2002

DOCUMENT-IDENTIFIER: US 20020187141 A1
TITLE: Polyspecific immunoconjugates and antibody compositiesfor targeting the multidrug resistant phenotype

Summary of Invention Paragraph:
[0029] As stated above, the polyspecific immunoconjugate comprises a diagnostic or therapeutic agent. A suitable diagnostic agent is selected from the group consisting of radioactive label, photoactive agent or dye, florescent label, enzyme label, bioluminescent label, chemiluminescent label, colloidal gold and paramagnetic ion. Moreover, a suitable radioactive label may be a .gamma.-emitter or a positron-emitter. Preferably, .gamma.-emitters have a gamma radiation emission peak in the range of 50-500 Kev, such as a radioisotope selected from the group consisting of .sup.99mTc, .sup.67Ga, .sup.123I, .sup.125I and .sup.131I.

Summary of Invention Paragraph:
[0030] A suitable therapeutic agent is selected from the group consisting of radioisotope, boron addend, immunomodulator, toxin, photoactive agent or dye, cancer chemotherapeutic drug, antiviral drug, antifungal drug, antibacterial drug, antiprotozoal drug and chemosensitizing agent. Moreover a suitable therapeutic radioisotope is selected from the group consisting of .alpha.-emitters, .beta.-emitters, .gamma.-emitters, Auger electron emitters, neutron capturing agents that emit .alpha.-particles and radioisotopes that decay by electron capture. Preferably, the radioisotope is selected from the group consisting of .sup.198Au, .sup.32P, .sup.125I, .sup.131I, .sup.90Y, .sup.186Re, .sup.188Re, .sup.67Cu and .sup.211At.

Summary of Invention Paragraph:
[0048] In such a detection method, the diagnostic agent is selected from the group consisting of radioactive label, photoactive agent or dye, fluorescent label and paramagnetic ion. Moreover, the biotin-binding molecule is avidin or streptavidin.

Summary of Invention Paragraph:
[0059] A suitable therapeutic agent is selected from the group consisting of radioisotope, boron addend, toxin, immunomodulator, photoactive agent or dye, cancer chemotherapeutic drug, antiviral drug, antifungal drug, antibacterial drug, antiprotozoal drug and a chemosensitizing agent. Again, the biotin-binding molecule is avidin or streptavidin.

Summary of Invention Paragraph:
[0064] Here, a suitable diagnostic agent selected from the group consisting of radioisotope, fluorescent label, chemiluminescent label, enzyme label, bioluminescent label and colloidal gold. Moreover, the antibody composite can further comprise biotin or a biotin-binding molecule.

Summary of Invention Paragraph:
[0069] A suitable diagnostic agent is selected from the group consisting of radioactive label, photoactive agent or dye, fluorescent label and paramagnetic ion.

Summary of Invention Paragraph:

[0077] Suitable diagnostic agents include radioisotopes, such as a .gamma.-emitter or a positron-emitter, and a photoactive agent or dye that is detected by laser-induced fluorescence.

Summary of Invention Paragraph:
[0079] (a) parenterally injecting the subject with a polyspecific immunoconjugate comprising (1) at least one antibody component that binds with a first epitope of a multidrug transporter protein, (2) at least one antibody component that binds with a first epitope of an antigen that is associated with a tumor or infectious agent, and (3) a photoactive agent or dye;

Summary of Invention Paragraph:
[0081] (c) treating sites of accretion of the polyspecific immunoconjugate to light, wherein the treatment activates the photoactive agent or dye.

Summary of Invention Paragraph:
[0109] As used herein, a diagnostic or therapeutic agent is a molecule or atom which is conjugated to an antibody moiety to produce a conjugate which is useful for diagnosis or for therapy. Examples of diagnostic or therapeutic agents include drugs, toxins, immunomodulators, chelators, boron compounds, photoactive agents or dyes, radioisotopes, fluorescent agents, paramagnetic ions or molecules and marker moieties.

Summary of Invention Paragraph:
[0166] Alternatively, an antibody composite can be conjugated with a diagnostic agent to form a polyspecific immunoconjugate. Antibody composites can be detectably labeled with any appropriate marker moiety, for example, a radioisotope, a fluorescent label, a chemiluminescent label, an enzyme label, a bioluminescent label or colloidal gold. Methods of making and detecting such detectably-labeled polyspecific immunoconjugates are well-known to those of ordinary skill in the art, and are described in more detail below.

Summary of Invention Paragraph:
[0167] The marker moiety can be a radioisotope that is detected by autoradiography. Isotopes that are particularly useful for the purpose of the present invention are .sup.3H, .sup.125I, .sup.131I, .sup.35S and .sup.14C .

Summary of Invention Paragraph:
[0176] The present invention also contemplates the use of antibody composites and polyspecific immunoconjugates for in vivo diagnosis. The method of diagnostic imaging with radiolabeled MAbs is well-known. In the technique of immunoscintigraphy, for example, antibodies are labeled with a gamma-emitting radioisotope and introduced into a patient. A gamma camera is used to detect the location and distribution of gamma-emitting radioisotopes. See, for example, Srivastava (ed.), RADIOLABELED MONOCLONAL ANTIBODIES FOR IMAGING AND THERAPY (Plenum Press 1988), Chase, "Medical Applications of Radioisotopes," in REMINGTON'S PHARMACEUTICAL SCIENCES, 18th Edition, Gennaro et al. (eds.), pp. 624-652 (Mack Publishing Co., 1990), Brown, "Clinical Use of Monoclonal Antibodies," in BIOTECHNOLOGY AND PHARMACY 227-49, Pezzuto et al. (eds.) (Chapman & Hall 1993), and Goldenberg, Calif.--A Cancer Journal for Clinicians 44: 43 (1994). For diagnostic imaging, radioisotopes may be bound to an antibody composite either directly, or indirectly by using an intermediary functional group. Useful intermediary functional groups include chelators such as ethylenediaminetetraacetic acid and diethylenetriaminepentaacetic acid. For example, see Shih et al., supra, and U.S. Pat. No. 5,057,313. Also, see Griffiths, U.S. Pat. No. 5,128,119 (1992).

Summary of Invention Paragraph:
[0177] The radiation dose delivered to the patient is maintained at as low a level as possible through the choice of isotope for the best combination of minimum half-life, minimum retention in the body, and minimum quantity of isotope which will

permit detection and accurate measurement. Examples of radioisotopes that can be bound to antibody composites and are appropriate for 30, diagnostic imaging include .gamma.-emitters and positron-emitters such as .sup.99mTc, .sup.67Ga, .sup.111In, .sup.123I, .sup.124I, .sup.125I, .sup.131I, .sup.51Cr, .sup.89Zr, .sup.18F and .sup.68Ga. Other suitable radioisotopes are known to those of skill in the art.

Summary of Invention Paragraph:
[0184] In a further variation of this method, improved detection can be achieved by conjugating multiple avidin/streptavidin or biotin moieties to a polymer which, in turn, is conjugated to an antibody component. Adapted to the present invention, antibody composites or polyspecific immunoconjugates can be produced which contain multiple avidin/streptavidin or biotin moieties. Techniques for constructing and using multiavidin/multistreptavidin and/or multibiotin polymer conjugates to obtain amplification of targeting are disclosed by Griffiths, international application No. PCT/US94/04295, which is incorporated by reference.

Summary of Invention Paragraph:
[0186] Polyspecific immunoconjugates which comprise a radiolabel also can be used to detect multidrug resistant (MDR) tumor cells, MDR HIV-infected cells or MDR infectious agents in the course of intraoperative and endoscopic examination using a small radiation detection probe. See Goldenberg U.S. Pat. No. 4,932,412, which is incorporated by reference. As an illustration of the basic approach, a surgical or endoscopy subject is injected parenterally with a polyspecific immunoconjugate comprising (1) at least one antibody component that binds with a first epitope of a multidrug transporter protein, (2) at least one antibody component that binds with a first epitope of an antigen that is associated with a tumor or infectious agent, and (3) a radioisotope. Subsequently, the surgically exposed or endoscopically accessed interior of the body cavity of the subject is scanned at close range with a radiation detection probe to detect the sites of accretion of the polyspecific immunoconjugate.

Summary of Invention Paragraph:
[0187] In a variation of this method, a photoactive agent or dye, such as dihematoporphyrin ether (Photofrin II), is injected systemically and sites of accretion of the agent or dye are detected by laser-induced fluorescence and endoscopic imaging. See Goldenberg, international application No. PCT/US93/04098, which is incorporated by reference. The prior art discloses imaging techniques using certain dyes that are accreted by lesions, such as tumors, and which are in turn activated by a specific frequency of light. These methods are described, for example, in Dougherty et al., Cancer Res. 38: 2628 (1978); Dougherty, Photochem. Photobiol. 45: 879 (1987); Doiron et al. (eds.), PORPHYRIN LOCALIZATION AND TREATMENT OF TUMORS (Alan Liss, 1984); and van den Bergh, Chem. Britain 22: 430 (1986), which are incorporated herein in their entirety by reference.

Summary of Invention Paragraph:
[0188] In a basic technique, a subject is injected parenterally with a polyspecific immunoconjugate comprising (1) at least one antibody component that binds with a first epitope of a multidrug transporter protein, (2) at least one antibody component that binds with a first epitope of an antigen that is associated with a tumor or infectious agent, and (3) a photoactive agent or dye. Sites of accretion are detected using a light source provided by an endoscope or during a surgical procedure.

Summary of Invention Paragraph:
[0193] For example, a therapeutic polyspecific immunoconjugate may comprise an .alpha.-emitting radioisotope, a .beta.-emitting radioisotope, a .gamma.-emitting radioisotope, an Auger electron emitter, a neutron capturing agent that emits .alpha.-particles or a radioisotope that decays by electron capture. Suitable radioisotopes include .sup.198Au, .sup.32P, .sup.125I, .sup.131I, .sup.90Y,

.sup.186Re, .sup.188Re, .sup.67Cu, .sup.211At, and the like.

Summary of Invention Paragraph:
[0194] As discussed above, a radioisotope can be attached to an antibody composite directly or indirectly, via a chelating agent. For example, .sup.67Cu, considered one of the more promising radioisotopes for radioimmunotherapy due to its 61.5 hour half-life and abundant supply of beta particles and gamma rays, can be conjugated to an antibody composite using the chelating agent, p-bromoacetamido-benzyl-tetraethylaminetetraac- etic acid (TETA). Chase, supra. Alternatively, .sup.90Y, which emits an energetic beta particle, can be coupled to an antibody composite using diethylenetriaminepentaacetic acid (DTPA). Moreover, a method for the direct radiolabeling of the antibody composite with .sup.131I is described by Stein et al., Antibody Immunoconj. Radiopharm. 4: 703 (1991).

Summary of Invention Paragraph:
[0198] In addition, therapeutically useful polyspecific immunoconjugates can be obtained by conjugating photoactive agents or dyes to an antibody composite. Fluorescent and other chromogens, or dyes, such as porphyrins sensitive to visible light, have been used to detect and to treat lesions by directing the suitable light to the lesion (cited above). In therapy, this has been termed photoradiation, phototherapy, or photodynamic therapy (Jori et al. (eds.), PHOTODYNAMIC THERAPY OF TUMORS AND OTHER DISEASES (Libreria Progetto 1985); van den Bergh, Chem. Britain 22: 430 (1986)). Moreover, monoclonal antibodies have been coupled with photoactivated dyes for achieving phototherapy (Mew et al., J. Immunol. 130: 1473 (1983); idem., Cancer Res. 45: 4380 (1985); Oseroff et al., Proc. Natl. Acad. Sci. USA 83: 8744 (1986); idem., Photochem. Photobiol. 46: 83 (1987); Hasan et al., Prog. Clin. Biol. Res. 288: 471 (1989); Tatsuta et al., Lasers Surg. Med. 9: 422 (1989); Pelegrin et al., Cancer 67: 2529 (1991)--all incorporated in their entirety herein by reference). However, these earlier studies did not include use of endoscopic therapy applications, especially with the use of antibody fragments or subfragments. Thus, the present invention contemplates the therapeutic use of polyspecific immunoconjugates comprising photoactive agents or dyes. The general methodology is described above in relation to the use of such polyspecific immunoconjugates for diagnosis.

Detail Description Paragraph:
Preparation of an Polyspecific Immunoconjugate Comprising a Radioisotope

Detail Description Paragraph:
[0234] A polyspecific immunoconjugate can be prepared in which a radioisotope is bound to one or more antibody components via a chelator. As an illustration, the antibody composite of Example 2 may be conjugated with either aminobenzyl diethylenetriaminepentaacetic acid (DTPA) or a derivative of DTPA containing the long-chain linker, --CSNH(CH.sub.2).sub.10NH.sub.2 (LC-DTPA). Briefly, the antibody composite (2.5 mg in about one milliliter of 50 mM acetate-buffered 0.9% saline [ABS; pH 5.3]) is oxidized in the dark by treatment with sodium metaperiodate (210 .mu.l of a 5.68 mg/ml solution) at 0.degree. C. for one hour. The reaction mixture is treated with ethylene glycol (20 .mu.l) to decompose the unreacted periodate and the oxidized antibody fragment is purified using a Sephadex G-50/80 column (Pharmacia; Piscataway, N.J.) equilibrated in PBS (pH 6.1). The oxidized fragment is then reacted with excess DTPA or LC-DTPA. After 40 hours at room temperature, the Schiff base is reduced by NaBH.sub.3CN. Conjugated antibody composite is then purified using a centrifuged size-exclusion column (Sephadex G-50/80) equilibrated in 0.1 M acetate (pH 6.5). The concentrations of antibody conjugates are determined by measuring absorbance at 280 nm.

CLAIMS:

5. The polyspecific immunoconjugate of claim 4, wherein said diagnostic agent is selected from the group consisting of radioactive label, photoactive agent or dye,

florescent label, enzyme label, bioluminescent label, chemiluminescent label, colloidal gold and paramagnetic ion.

9. The polyspecific immunoconjugate of claim 4, wherein said therapeutic agent is selected from the group consisting of radioisotope, boron addend, immunomodulator, toxin, photoactive agent or dye, cancer chemotherapeutic drug, antiviral drug, antifungal drug, antibacterial drug, antiprotozoal drug and chemosensitizing agent.

10. The polyspecific immunoconjugate of claim 9, wherein said radioisotope is selected from the group consisting of .alpha.-emitters, .beta.-emitters, .gamma.-emitters, Auger electron emitters, neutron capturing agents that emit a particles and radioisotopes that decay by electron capture.

11. The polyspecific immunoconjugate of claim 9, wherein said radioisotope is selected from the group consisting of .sup.198Au, .sup.32P, .sup.125I, .sup.131I, .sup.90Y, .sup.186Re, .sup.188Re, .sup.67Cu and .sup.211At.

19. The method of claim 18, wherein said therapeutic agent is selected from the group consisting of radioisotope, boron addend, toxin, immunomodulator, photoactive agent or dye, cancer chemotherapeutic drug, antiviral drug, antifungal drug, antibacterial drug, antiprotozoal drug and a chemosensitizing agent.

20. The method of claim 19, wherein said radioisotope is selected from the group consisting of .alpha.-emitters, .beta.-emitters, .gamma.-emitters, Auger electron emitters, neutron capturing agents that emit .alpha.-particles and radioisotopes that decay by electron capture.

21. The method of claim 19, wherein said radioisotope is selected from the group consisting of .sup.198Au, .sup.32P, .sup.125I, .sup.131I, .sup.90Y, .sup.186Re, .sup.188Re, .sup.67Cu and .sup.211At.

34. The method of claim 33, wherein said diagnostic agent is selected from the group consisting of radioactive label, photoactive agent or dye, fluorescent label and paramagnetic ion.

44. The method of claim 43, wherein said therapeutic agent is selected from the group consisting of radioisotope, boron addend, toxin, immunomodulator, photoactive agent or dye, cancer chemotherapeutic drug, antiviral drug, antifungal drug, antibacterial drug, antiprotozoal drug and a chemosensitizing agent.

45. The method of claim 44, wherein said radioisotope is selected from the group consisting of .alpha.-emitters, .beta.-emitters, .gamma.-emitters, Auger electron emitters, neutron capturing agents that emit .alpha.-particles and radioisotopes that decay by electron capture.

46. The method of claim 44, wherein said radioisotope is selected from the group consisting of .sup.198Au, .sup.32P, .sup.125I, .sup.131I, .sup.90Y, .sup.186Re, .sup.188Re, .sup.67Cu and .sup.211At.

51. The method of claim 50, wherein said antibody composite further comprises a diagnostic agent selected from the group consisting of radioisotope, fluorescent label, chemiluminescent label, enzyme label, bioluminescent label and colloidal gold.

57. The method of claim 56, wherein said diagnostic agent is selected from the group consisting of radioactive label, photoactive agent or dye, fluorescent label and paramagnetic ion.

65. The method of claim 64, wherein said therapeutic agent is selected from the

group consisting of radioisotope, boron addend, toxin, immunomodulator, photoactive agent or dye, cancer chemotherapeutic drug, antiviral drug, antifungal drug, antibacterial drug, antiprotozoal drug and a chemosensitizing agent.

66. The method of claim 65, wherein said radioisotope is selected from the group consisting of .alpha.-emitters, .beta.-emitters, .gamma.-emitters, Auger electron emitters, neutron capturing agents that emit .alpha.-particles and radioisotopes that decay by electron capture.

67. The method of claim 65, wherein said radioisotope is selected from the group consisting of .sup.198Au, .sup.32P, .sup.125I, .sup.131I, .sup.90Y, .sup.186Re, .sup.188Re, .sup.67Cu and .sup.211At.

72. The method of claim 71, wherein said diagnostic agent is a radioisotope.

73. The method of claim 72, wherein said radioisotope is a .gamma.-emitter or a positron-emitter.

74. The method of claim 72, wherein said diagnostic agent is a photoactive agent or dye.

75. The method of claim 74, wherein said photoactive agent or dye is detected by laser-induced fluorescence.

92. A method for treating a subject having a multidrug resistant disease caused by a tumor or infectious agent, said method comprising the steps of: (a) parenterally injecting the subject with a polyspecific immunoconjugate comprising (1) at least one antibody component that binds with a first epitope of a multidrug transporter protein, (2) at least one antibody component that binds with a first epitope of an antigen that is associated with a tumor or infectious agent, and (3) a photoactive agent or dye; (b) surgically exposing or endoscopically accessing the interior of the body cavity of said subject;, and (c) treating sites of accretion of said polyspecific immunoconjugate to light, wherein said treatment activates said photoactive agent or dye.

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L15: Entry 16 of 87 File: PGPB Nov 7, 2002

DOCUMENT-IDENTIFIER: US 20020164648 A1
TITLE: Methods and compositions for delivery and retention of active agents to lymph nodes

Summary of Invention Paragraph:
[0021] Methods for detecting sentinel lymph nodes have been described. In one method microcolloidal particles labeled with a radioisotope are administered interstitially proximal to the tumor site and scintigraphic scans or radio-guided probes are used to locate the site(s) of maximum radioactivity. This method is described, for example, in Van der Veen et al., Br J Surg 81(12):1769-1770, 1994; Krag et al., Surg Oncol 2:335-339, 1993; Veronesi et al., Lancet 349(9069):1864-1867, 1997, all of which are incorporated herein in their entirety by reference. In another method, vital blue dye is injected peri-tumor, as described, for example, in Morton et al., Surg Oncol Clin N Am 1:247-59, 1992 and Arch Surg 127(4):392-399, 1992, incorporated herein in their entirety by reference. An intraoperative method for detecting sentinel lymph nodes using both radiolabeled colloid and vital blue dye has also been described, for example, in Cox et al., Ann Surg 227(5):645-653, 1998, incorporated herein in its entirety by reference. In this method radiolabeled colloid is injected around the periphery of a tumor site one to six hours prior to an operative procedure. Immediately before the operative procedure, vital blue dye is injected peri-tumor. The vital blue dye stains afferent lymphatic channels to aid in visual localization of the sentinel lymph node. Prior to skin incision, a hand-held gamma-detection probe is used to localize the sentinel lymph node. After incision, the gamma probe is used to guide localization of the sentinel lymph node. See, for example, Kotz, J Nucl Med 39(12):13N-21N, 1998; Krag et al., N Engl J Med 339(14):941-946, 1998; Reintgen, J Nucl Med 39(12):22N-36N, 1998, all of which are incorporated herein in their entirety by reference.

Summary of Invention Paragraph:
[0022] Injection of a radiolabeled colloid to detect the sentinel lymph node by a radioactive probe has been used in conjunction with injection of blue dye to visualize the sentinel lymph nodes. A problem with this approach is that the radiolabeled colloid and the blue dye do not move through the lymphatic system at the same rate. The blue dye is absorbed rapidly from its site of injection and readily passes through lymph nodes. In contrast, the radiolabeled colloid is absorbed more slowly, takes time to accumulate in the lymph node, and does not significantly pass through the first lymph node encountered to other lymph nodes. Consequently, the timing of the localizing surgical procedure is difficult because simultaneous accumulation of blue dye and radiolabeled colloid at the sentinel node requires very different injection times for the blue dye and radiolabeled colloid.

Summary of Invention Paragraph:
[0026] In one embodiment, the present invention features a ligand/anti-ligand system and colloids that are captured by draining lymph nodes when administered to a subject in vivo. Ligand or anti-ligand may be conjugated to the colloid. The ligand may be, for example, biotin The anti-ligand may be, for example, avidin.

Summary of Invention Paragraph:
[0027] In another embodiment, the invention features methods of delivering and retaining an active agent at targeted lymph nodes in a mammal. The methods comprise

the steps of (a) administering to a mammal a first composition comprising ligand conjugated to a colloid, and (b) administering to a mammal a second composition comprising anti-ligand in which the anti-ligand binds to the ligand. The anti-ligand may be administered proximal to the site of the colloid-ligand conjugate administration. After the anti-ligand binds the ligand of the colloid-ligand conjugate, the aggregated colloid complex may be retained at the lymph node(s) draining the areas of interest.

Summary of Invention Paragraph:
[0030] In yet another embodiment the invention provides a method and composition for delivering and retaining an active agent at the sentinel lymph node(s) comprising the steps of (a) administering to a mammal a first composition comprising ligand conjugated to a colloid, and (b) administering to a mammal a second composition comprising anti-ligand in which the anti-ligand binds to the ligand. The colloid may comprise an active agent, in particular, a blue dye as a detection means. Anti-ligand, with or without an active agent, that binds to the ligand of the ligand-colloid-blue dye composition, may be administered simultaneously or shortly after the ligand-colloid-blue dye composition is administered to a mammal. The preferred administration method is by subcutaneous injection.

Summary of Invention Paragraph:
[0032] The invention may be useful in delivering and retaining one or more therapeutic agents at targeted lymph nodes. The invention may also be useful in delivering and retaining one or more diagnostic agents, such as dyes or radioisotopes, at targeted lymph nodes.

Summary of Invention Paragraph:
[0041] As defined herein, a "ligand" is a molecule conjugated to the colloid with high affinity for the anti-ligand. Biotin is an example of a ligand useful in the present invention.

Summary of Invention Paragraph:
[0049] A pharmaceutically or therapeutically active agent or diagnostic agent ("the payload"), including radionuclides, drugs, anti-tumor agents, toxins, dyes, contrast media, and the like. The active agent may be associated with the colloid particles by any well-known technique, but should be in such a way that the active agent remains associated with the colloid particle until at least the point of uptake of the particle by the lymph node.

Summary of Invention Paragraph:
[0055] A composition comprising anti-ligand, which may or may not be conjugated to an active agent, bound to ligand conjugated or bound to a colloid, which may or may not be complexed with an active agent.

Summary of Invention Paragraph:
[0057] A composition comprising anti-ligand bound to ligand, which is conjugated or bound to colloid.

Summary of Invention Paragraph:
[0066] In an embodiment of the method of the present invention, the ligand-colloid-active agent can be administered as a single injection or in divided doses. For example, simultaneous with the ligand-colloid composition or after 2 hours, more preferably at less than 30 minutes and even at less than 10 minutes, a dose of anti-ligand, with or without an active agent, is administered. The anti-ligand composition can be given as a single injection or in divided doses; administering the anti-ligand in two doses is preferred in certain circumstances. The ligand-colloid and anti-ligand compositions are administered by subcutaneous, subdermal, submucosal, intraperitoneal, or intrapleural injection. Within one hour of the last injection, detection of lymph nodes containing the aggregated colloid complex is

accomplished. If a radiolabeled detection agent is encapsulated in or attached to the colloid or attached to anti-ligand, detection of the lymph nodes is accomplished using for example, planar and single-photon emission computed tomography scans made with a gamma camera equipped with the appropriate collimator and selecting the appropriate energy windows for the detection isotope being used, such as 140 keV for Technetium-99m. If blue dye is encapsulated in the colloid, the lymph nodes can be visually detected.

Summary of Invention Paragraph:
[0071] An advantage of the present invention is the flexibility of the system. For example, when a biotin-liposome-avidin complex is utilized, the complex is strongly retained in the targeted lymph node for a prolonged period, at least several days, until it is metabolized. If Technetium-99m, whose half-life is 6 hours, is employed as an active agent, it can still be imaged at least 20 hours after administration. If blue dye is employed as an active agent, lymph nodes may be visually detected at least two weeks after administration. X-ray and computerized axial tomography contrast agents may be detected for a prolonged time period, similar to that for detection of blue dye.

Summary of Invention Paragraph:
[0077] (1) administering to a mammal a first conjugate comprising ligand conjugated to a colloid; and associated with vital blue dye and which may further contain another active agent, and ligand, for example, biotin;

Summary of Invention Paragraph:
[0079] The colloid may be associated with a detection agent, such as a radioisotope or dye. The ligand may be, for example, biotin. The anti-ligand, which may or may not be associated with an active agent, may be, for example, avidin. The anti-ligand may be administered simultaneously or immediately after administration of the colloid-ligand composition.

Summary of Invention Paragraph:
[0080] Yet another embodiment of the invention provides a composition comprising ligand conjugated to a colloid containing a radioactive label and a readily-visualized dye.

Summary of Invention Paragraph:
[0084] These techniques provide information regarding detection of neoplastic involvement, particularly of inaccessible nodes in subjects with malignant diseases and can also be applied in other infectious and inflammatory conditions. Knowledge on the size of the node and the filling of nodes can also be instructive. The particles so directed to the lymph nodes in diagnostic applications will contain suitable contrast or imaging agents such as ferromagnetic materials such as iron oxide, perfluorochemicals such as perfluorooctylbromide, dyes, or gamma emitting radiolabels such as Technetium-99m, Indium-111, Gallium-67, Thallium-201, Iodine-123, 125, or 131, positron emitting radiolabels such as Fluorine-18.

Detail Description Paragraph:
[0110] Kits comprising (1) ligand conjugated to a colloid containing an active agent, and (2) anti-ligand with or without an active agent comprise another aspect of the present invention. The detection/therapeutic kits comprising the active agents disclosed herein will generally contain, in suitable container means, a detection- or therapeutically-effective amount of an active agent. The kit may have a single container means that contains the ligand-targeting colloid-active agent, or it may have distinct container means for each compound.

Detail Description Paragraph:
[0119] B--photoactivated dyes for detection or therapy;

Detail Description Paragraph:

[0122] E--dyes for visual detection;

Detail Description Paragraph:
[0128] Any of a variety of therapeutics may be encapsulated in the colloids or conjugated to the surface of the colloids. Many pharmaceutical compositions are known which have cytotoxic effects on cells. They are to be found in compendia of drugs, such as the Merck Index, Goodman and Gilman, and the like, and in the references cited above. Any such pharmaceutical composition can be conjugated to anti-ligand or loaded into the ligand-colloid by conventional means well known in the art.

Detail Description Paragraph:
[0130] Examples of known cytotoxic agents useful in the present invention are listed in Goodman et al., The Pharmacological Basis of Therapeutics, 6th Ed., Gilman et al., (eds.), Macmillan Publishing Co., New York, 1980, incorporated herein in its entirety by reference. These include taxol; nitrogen mustards, such as mechlorethamine, cyclophosphamide, melphalan, uracil mustard and chlorambucil; ethylenimine derivatives, such as thiotepa; alkyl sulfonates, such as busulfan; nitrosoureas, such as carmustine, lomustine, semustine and streptozocin; triazenes, such as dacarbazine; folic acid analogs, such as methotrexate; pyrimidine analogs, such as fluorouracil, cytarabine and azaribine; purine analogs, such as mercaptopurine and thioguanine; vinca alkaloids, such as vinblastine and vincristine; antibiotics, such as dactinomycin, daunorubicin, doxorubicin, bleomycin, mithramycin and mitomycin; enzymes, such as L-asparaginase; platinum coordination complexes, such as cisplatin; substituted urea, such as hydroxyurea; methyl hydrazine derivatives, such as procarbazine; antibiotics; anti-virals; vaccines; and photodynamic dyes.

Detail Description Paragraph:
[0135] Radioisotopes may also be used as therapeutic agents. Any conventional method of radiolabeling which is suitable for labeling isotopes for in vivo use will be generally suitable for labeling therapeutic agents according to the present invention.

Detail Description Paragraph:
[0138] Detection agents of use in the present invention include radioisotopes and dyes. Any conventional method of radiolabeling which is suitable for labeling isotopes for in vivo use will be generally suitable for labeling detection agents according to the present invention. Internal detection procedures include intraoperative, intravascular or endoscopic, including laproscopic, techniques, both surgically invasive and noninvasive.

Detail Description Paragraph:
[0140] Suitable radioisotopes for the methods of the present invention include: Actinium-225, Astatine-211, Iodine-123, Iodine-125, Iodine-126, Iodine-131, Iodine-133, Bismuth-212, Bromine-77, Indium-111, Indium-113m, Gallium-67, Gallium-68, Ruthenium-95, Ruthenium-97, Ruthenium-103, Ruthenium-105, Mercury-107, Mercury-203, Rhenium-186, Rhenium-188, Tellurium-121m, Tellurium-122m, Tellurium-125m, Thulium-165, Thulium-167, Thulium-168, Technetium-99m, Fluorine-18, Silver-111,Platinum-197, Palladium-109, Copper-67, Phosphorus-32, Phosphorus-33, Yttrium-90, Scandium-47, Samarium-153, Lutetium-177, Rhodium-105, Praseodymium-142, Praseodymium-143, Terbium-161, Holmium-166, Gold-199, Cobalt-57, Cobalt-58, Chromium-51, Iron-59, Selenium-75, Thallium-201, and Ytterbium-169. The most preferred radioisotope for use in the current invention is Technetium-99m. Preferably the radioisotope will emit a particle or ray in the 10-7,000 keV range, more preferably in the 50-1,500 keV range, and most preferably in the 80-250 keV range.

Detail Description Paragraph:
[0141] Isotopes preferred for external imaging include: Iodine-123, Iodine-131, Indium-111, Gallium-67, Ruthenium-97, Technetium-99m, Cobalt-57, Cobalt-58,

Chromium-51, Iron-59, Selenium-75, Thallium-201, and Ytterbium-169. Technetium-99m is the most preferred radioisotope for external imaging in the present invention.

Detail Description Paragraph:
[0143] Dyes may also be used as detection agents. In order to aid with localization of the sentinel lymph node for a tumor, blue dye has been injected around the tumor. The blue dye travels into the lymphatic system and through the sentinel lymph node. While this permits visualization of lymph nodes, for example, during surgical procedures, it does not permit detection of the sentinel lymph node because the blue dye does not localize at the first lymph node encountered, but passes on to lymph nodes further along the lymph node chain.

Detail Description Paragraph:
[0144] Incorporation of blue dye with the colloid of the aggregated colloid complex of the present invention provides for retention of the blue dye at the first lymph node encountered, or in the chain of draining lymph nodes, depending upon the timing of administration of the anti-ligand-active agent.

Detail Description Paragraph:
Methods for Preparing Biotin-Colloid Conjugates Encapsulating Blue Dye

Detail Description Paragraph:
[0147] Methods for preparing biotin-colloid conjugates encapsulating blue dye are known to those skilled in the art. A preferred method is described below.

Detail Description Paragraph:
[0148] Liposomes encapsulating blue dye were comprised of the same lipids as for the biotin-liposomes. The liposomes were processed in an identical fashion as listed above except patent blue violet dye (Sigma, St Louis, Mo.; CI 42045) was included during processing in the following manner: 1). The dry sugar-lipid preparation was rehydrated with Dulbeccco's phosphate buffered saline pH 6.3 containing 200 mM GSH and 10 mg/ml of blue dye at a lipid concentration of 102 mM. 2) Immediately before extrusion, the liposome solution was diluted at a volume/volume ratio of 1 part lipid suspension to 2 parts Dulbecco's phosphate buffered saline containing 100 mM GSH, 150 mM sucrose and 10 mg/ml of blue dye.

Detail Description Paragraph:
Methods for Radiolabeling Ligand-Colloid Conjugates Alone or Encapsulating Blue Dye

Detail Description Paragraph:
[0149] Methods for radiolabeling ligand-colloid conjugates, such as biotin-colloid conjugates, which may encapsulate blue dye, are known to those skilled in the art. A preferred method is described below.

Detail Description Paragraph:
[0150] The Technetium-99m (.sup.99mTc) carrier found most preferable is an alkylenepropyleneamine oxime that complexes with .sup.99mTc and can be purchased as a lyophilized preparation (Ceretec.TM., Nycomed-Amersham, Arlington Hgts, Ill.). In this form, HMPAO is mixed with sterile eluate from a .sup.99mTc-generator The generator eluate may be adjusted to a radioactive concentration of between 037-1.11 GBq (10-30 mCi) in 5 ml by dilution with preservative free, nonbacteriostatic saline prior to mixing with 0.5 mg of HMPAO. The .sup.99mTc complex forms almost immediately and is incubated for 5 min at room temperature. This mixture of .sup.99mTc-HMPAO (0.5 ml, 1 mCi) was then incubated with 1 ml (102 mM of lipid) of either biotin-liposomes containing GSH alone or biotin-liposomes coencapsulating GSH and blue dye prepared as described above. The .sup.99mTc-HMPAO-liposome mixture was incubated for 15-30 min at room temperature with intermittent swirling. The radiolabeled liposomes were then separated from any free .sup.99mTc by passage over a Sephadex G-25 column (PD10 column, Pharmacia Biotech, Uppsala, Sweden)

equilibrated with Dulbecco's phosphate buffered saline pH 6.3. Labeling efficiencies were checked by determining the activity before and after column separation of the .sup.99mTc-biotin-liposomes using a dose calibrator (Radix, Houston, Tex.). Labeling efficiencies averaged 97% for biotin-liposomes containing GSH and 92% for biotin-liposomes coencapsulating GSH and blue dye. Postcolumn preparations of the .sup.99mTc-biotin-liposomes were used immediately for injection.

Detail Description Paragraph:
[0152] When the active agent is a radioisotope for detection or therapy, the preferred method of preparation will depend, for example, on the isotope chemistry. Methods for conjugating anti-ligand, for example, avidin, to a detection or therapeutic agent include the following: (a) the chloramine-T or Bolton-Hunter procedures for conjugating iodine, (b) the procedures described by Griffiths et al., Cancer Res 51(17):4594-4602, 1991, or Fritzberg et al., U.S. Pat. No. 5,120,526, to conjugate Technetium or Rhenium (c) through bifunctional chelating agents as described by Meares et al., Br J Cancer Suppl 10:21-26, 1990, to conjugate metallic nuclides. Additionally, avidin can be bound to dendrimers by procedures described for amino-containing proteins as described by Hnatowich et al., J Nucl Med 28(8):1294-1302, 1987. The disclosures of the above publications are incorporated herein in their entirety by reference.

Detail Description Paragraph:
[0157] The scintigram is normally taken by a gamma imaging camera having one or more windows for detection of energies in the 50-600 keV range. Use of radioisotopes with higher energy, beta, or positron emissions would entail use of imaging cameras with the appropriate detectors, all of which are conventional in the art.

Detail Description Paragraph:
[0161] Magnetic resonance imaging (MRI) is effected in an analogous manner to scintigraphic imaging except that the imaging agents will contain magnetic resonance (MR) enhancing species rather than radioisotopes. It will be appreciated that the magnetic resonance phenomenon operates on a different principle from scintigraphy. Normally, the signal generated is correlated with the relaxation times of the magnetic moments of protons in the nuclei of the hydrogen atoms of water molecules in the region to be imaged. The magnetic resonance image enhancing agent acts by increasing the rate of relaxation, thereby increasing the contrast between water molecules in the region where the imaging agent accretes and water molecules elsewhere in the body. However, the effect of the agent is to decrease both T.sub.1 and T.sub.2, the former resulting in greater contrast while the latter results in lesser contrast. Accordingly, the phenomenon is concentration-dependent, and there is normally an optimum concentration of a paramagnetic species for maximum efficacy. This optimal concentration will vary with the particular agent used, the locus of imaging, the mode of imaging, i.e., spin-echo, saturation-recovery, inversion-recovery and/or various other strongly TI-dependent or T.sub.2-dependent imaging techniques, and the composition of the medium in which the agent is dissolved or suspended. These factors, and their relative importance are known in the art. See, e.g., Okuhata, Adv Drug Delivery Rev 37:121-137, 1999; Pykett, Sci Am, 246(5):78-88, 1982; Runge et al., Am J Roentgeno, 141(6):1209-1215, 1983, all of which are incorporated herein in their entirety by reference.

Detail Description Paragraph:
[0172] Vaccine adjuvants are agents when given in combination with an antigen, greatly increase the immune response to the antigen. Vaccine adjuvants are essentially antigen delivery systems, however, the mechanisms and locations involved in the delivery of the antigen are poorly understood. Most common adjuvants are colloids. Typical colloids used are aluminum hydroxide colloids and liposome colloids. (See Theory and Practical Application of Adjuvants. Stewart-Tull (ed), John Wiley & Sons Ltd., Chichester, England, 1995, incorporated herein by

reference.) The most recent information indicates that antigen delivery to the lymph node and induction of lymph node hypercellularity are important aspects of adjuvant function. Lindblad, in Theory and Practical Application of Adjuvants, Stewart-Tull (ed), John Wiley & Sons Ltd., Chichester, England, pg. 21-35, 1995 and Gregoriadis, in Theory and Practical Application of Adjuvants, Stewart-Tull (ed), John Wiley & Sons Ltd., Chichester, England, pg. 145-169, 1995, incorporated herein in their entirety by reference. Since the essential nature of how vaccine adjuvants work is poorly understood, most vaccine development is conducted by trial and error. These trial and error techniques are inefficient and costly. Much effort is currently being focused on understanding how vaccines work. This work has been spurred by the effort to develop an effective vaccine for treatment and prevention of HIV infection and as an immune stimulant for cancer therapy. Even though vaccine adjuvants are clearly antigen delivery vehicles, virtually no studies have used isotopes or imaging or other detection agents such as dyes to study their biodistribution in the body after administration. If lymph node delivery is important, it will be obvious that the colloid-ligand-anti-ligand system described herein will be very useful for enhancing immune response to an antigen which is delivered to the lymph nodes by this system.

Detail Description Paragraph:
Visual Marking of Sentinel Lymph Nodes with Blue Dye

Detail Description Paragraph:
[0182] Biotin-liposomes labeled with .sup.99mTc can encapsulate blue dye for visually marking the first lymph node encountered. The blue dye can also be considered as an example of drug delivery to a lymph node. Other drugs such as anticancer agents, antiviral agents, vaccines, photodynamic dyes, antibiotics, and therapeutic radionuclides, could also be delivered instead of blue dye.

Detail Description Paragraph:
[0183] In this study, 0.3 ml of .sup.99mTc-biotin-liposomes encapsulating blue dye was subcutaneously injected into both foot pads of 6 rabbits. Immediately after injection of the liposomes, 5 mg of avidin was subcutaneously injected into the right foot 2-3 cm proximal to the liposome injection. This study was an asymmetric study because only the right foot was injected with the avidin. Rabbits were imaged for the first hour and at 20 hr after liposome injection. At 20 hr, rabbits were sacrificed and tissue samples were counted in a scintillation well counter.

Detail Description Paragraph:
[0186] To assess the effect of repeat injections on the avidin-induced retention of biotin-liposomes in the popliteal lymph nodes, a study was performed with .sup.99mTc-biotin-liposomes encapsulating blue dye. These studies were asymmetric and performed in the same manner as Example 13 studies, except that the same group of rabbits (n=4) received repeat injections at baseline, 2 wk and 4 wk. Liposomes were injected into the dorsum of both feet with avidin injected 2 cm proximal on the right foot only. Imaging was performed for the first hour and at 20 hr after liposome injection. Biodistribution was performed by scintigraphic imaging alone since tissue sampling was not possible until the end of the third study in each rabbit.

Detail Description Paragraph:
[0192] To determine if liposomes injected into the peritoneum, followed 30 min later by avidin injected into the peritoneum, would target the lymph nodes that receive lymph that drains from the peritoneum, 2 ml of .sup.99mTc-biotin-liposomes encapsulating blue dye were injected into the peritoneum of experimental (n=4) and control rats (n--4). Thirty minutes after liposome injection, 5 mg of avidin in 1 ml of saline was injected into the peritoneum of the experimental group, while the controls received no avidin.

CLAIMS:

9. The method of claim 8, wherein the active agent is chosen from the group consisting of diagnostic agents, therapeutic agents, photoactivated dyes, cytotoxic agents, biological response modifiers, hormone suppressants, prodrugs, dyes for visual detection, radiosensitizers, radioprotectors, DNA, RNA, antigens, radioisotopes and neutron capture isotopes.

10. The method of claim 9, wherein the active agent is chosen from the group consisting of radioisotopes and dyes.

11. The method of claim 9, wherein the active agent is chosen from the group consisting of diagnostic agents and dyes for visual detection.

12. The method of claim 9, wherein the active agent is chosen from the group consisting of photoactivated dyes, cytotoxic agents, biological response modifiers, hormone suppressants, prodrugs, radiosensitizers, radioprotectors, DNA, RNA, and neutron capture agents.

17. The method of claim 16, wherein the active agent is chosen from the group consisting of radioisotopes and dyes.

19. The method of claim 18, wherein the detection agent comprises a radioisotope or dye.

25. A composition comprising: a) ligand conjugated to colloid, and b) anti-ligand.

28. The composition of claim 25, wherein the colloid comprises: a) glutathione, b) .sup.99mTc-HMPAO; and c) blue dye.

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L15: Entry 23 of 87 File: PGPB Mar 21, 2002

DOCUMENT-IDENTIFIER: US 20020034511 A1
TITLE: Pretargeting methods and compounds

Detail Description Paragraph:
[0050] These characteristics are particularly problematic with human radioimmunotherapy. In human clinical trials, the long circulating half-life of radioisotope bound to whole antibody causes relatively large doses of radiation to be delivered to the whole body. In particular, the bone marrow, which is very radiosensitive, is the dose-limiting organ of non-specific toxicity.

Detail Description Paragraph:
[0051] In order to decrease radioisotope exposure of non-target tissue, potential targeting moieties generally have been screened to identify those that display minimal non-target reactivity, while retaining target specificity and reactivity. By reducing non-target exposure (and adverse non-target localization and/or toxicity), increased doses of a radiotherapeutic conjugate may be administered; moreover, decreased non-target accumulation of a radiodiagnostic conjugate leads to improved contrast between background and target.

Detail Description Paragraph:
[0052] Therapeutic drugs, administered alone or as targeted conjugates, are accompanied by similar disadvantages. Again, the goal is administration of the highest possible concentration of drug (to maximize exposure of target tissue), while remaining below the threshold of unacceptable normal organ toxicity (due to non-target tissue exposure). Unlike radioisotopes, however, therapeutic drugs need to be taken into a target cell to exert a cytotoxic effect. In the case of targeting moiety-therapeutic drug conjugates, it would be advantageous to combine the relative target specificity of a targeting moiety with a means for enhanced target cell internalization of the targeting moiety-drug conjugate.

Detail Description Paragraph:
[0151] 1) increased tumor uptake in that more of the radioisotope will be targeted to the previously localized targeting moiety-streptavidin; and

Detail Description Paragraph:
[0152] 2) increased tumor retention, if biotin is more stably bound to the radioisotope. In addition, the linkage between DOTA and biotin may also have a significant impact on biodistribution (including normal organ uptake, target uptake and the like) and pharmacokinetics.

Detail Description Paragraph:
[0288] The use of this aspect of the present invention also facilitates the delivery of higher molecular weight therapeutic agent-bearing conjugates to target sites characterized by a three dimensional cellular array. For example, one or more ligand or anti-ligand molecules as well as a plurality of therapeutic agent molecules may be conjugated to a polymer to form an entity of the following formula:

Detail Description Paragraph:
[0303] Some polymers useful in the practice of this permeability enhancing aspect

of the present invention serve solely as a carrier for multiple therapeutic agents. Preferred polymers also direct the biodistribution of the ligand or anti-ligand and therapeutic agents to which the polymer is bound to renal rather than, for example, hepatobiliary excretion. For many administered therapeutic agents (e.g., radionuclides), renal excretion is preferred, especially for therapeutic protocols.

Detail Description Paragraph:
[0484] Both iodobiotin derivatives 2 exhibited .gtoreq.95% binding to immobilized avidin. Incubation of the products 2 with mouse serum resulted in no loss of the ability of 2 to bind to immobilized avidin. Biodistribution studies of 2 in male BALB/c mice showed rapid clearance from the blood (similar to .sup.186Re-chelate-biotin conjugates described above). The radioiodobiotin 2 had decreased hepatobiliary excretion as compared to the .sup.186Re-chelate-biotin conjugate; urinary excretion was increased as compared to the .sup.186Re-chelate-biotin conjugate. Analysis of urinary metabolites of 2 indicated deiodination and cleavage of the biotin amide bond; the metabolites showed no binding to immobilized avidin. In contrast, metabolites of the .sup.186Re-chelate-biotin conjugate appear to be excreted in urine as intact biotin conjugates. Intestinal uptake of 2 is <50% that of the .sup.186Re-chelate-biotin conjugate. These biodistribution properties of 2 provided enhanced whole body clearance of radioisotope and indicate the advantageous use of 2 within pretargeting protocols.

Detail Description Paragraph:
[0491] A .sup.99mTc-chelate-biotin conjugate is prepared as in Example II, above. The NR--LU-13-avidin conjugate is administered to a recipient and allowed to clear from the circulation. One of ordinary skill in the art of radioimmunoscintigraphy is readily able to determine the optimal time for NR--LU-13-avidin conjugate tumor localization and clearance from the circulation. At such time, the .sup.99mTc-chelate-biotin conjugate is administered to the recipient. Because the .sup.99mTc-chelate-biotin conjugate has a molecular weight of .apprxeq.1,000, crosslinking of NR--LU-13-avidin molecules on the surface of the tumor cells is dramatically reduced or eliminated. As a result, the .sup.99mTc diagnostic agent is retained at the tumor cell surface for an extended period of time. Accordingly, detection of the diagnostic agent by imaging techniques is optimized; further, a lower dose of radioisotope provides an image comparable to that resulting from the typical three-step pretargeting protocol.

Detail Description Paragraph:
[0690] Mice bearing LS-180 colon tumor xenografts were injected with 200 micrograms NR--LU-10 antibody-streptavidin (MAb-StrAv) conjugate at time 0, which was allowed to prelocalize to tumor for 22 hours. At that time, 20 micrograms of AO-Bt was administered to one group of animals. Two hours later, 90 micrograms of a radioisotope-bearing, ligand-containing small molecule (PIP-biotin-dextran prepared as discussed in part B hereof) was administered to this group of mice and also to a group which had not received AO-Bt. The results of this experiment with respect to radiolabel uptake in tumor and clearance from the blood indicated that tumor-targeting of the radiolabeled biotin-containing conjugate was retained while blood clearance was enhanced, leading to an overall improvement in amount delivered to target/amount located in serum. The AUC tumor/AUC blood with clearing agent was 6.87, while AUC tumor/AUC blood without clearing agent was 4.45. Blood clearance of the circulating MAb-StrAv conjugate was enhanced with the use of clearing agent. The clearing agent was radiolabeled in a separate group of animals and found to bind directly to tumor at very low levels (1.7 pmol/g at a dose of 488 total pmoles (0.35% ID/g), indicating that it does not significantly compromise the ability of tumor-bound MAb-StrAv to bind subsequently administered radiolabeled ligand.

Detail Description Paragraph:
[0697] Tumored mice injected with MAb-StrAv at time 0 as above; 50 micrograms of AO-Bt at time 22 hours; and 545 microcuries of I-131-PIP-biocytin at time 25 hours.

Whole body radiation was measured and compared to that of animals that had not received clearing agent. 50 micrograms of AO-Bt was efficient in allowing the injected radioactivity to clear from the animals unimpeded by binding to circulating MAb-StrAv conjugate. Tumor uptake of I-131-PIP-biocytin was preserved at the 50 microgram clearing agent dose, with AUC tumor/AUC blood of 30:1 which is approximately 15-fold better than the AUC tumor/AUC blood achieved in conventional antibody-radioisotope therapy using this model.

L15: Entry 36 of 87 File: USPT Sep 11, 2001

DOCUMENT-IDENTIFIER: US 6287536 B1
TITLE: Two-step pretargeting methods using improved bidtin-active agent conjugates

Detailed Description Text (21):
These characteristics are particularly problematic with human radioimmunotherapy. In human clinical trials, the long circulating half-life of radioisotope bound to whole antibody causes relatively large doses of radiation to be delivered to the whole body. In particular, the bone marrow, which is very radiosensitive, is the dose-limiting organ of non-specific toxicity.

Detailed Description Text (22):
In order to decrease radioisotope exposure of non-target tissue, potential targeting moieties generally have been screened to identify those that display minimal non-target reactivity, while retaining target specificity and reactivity. By reducing non-target exposure (and adverse non-target localization and/or toxicity), increased doses of a radiotherapeutic conjugate may be administered; moreover, decreased non-target accumulation of a radiodiagnostic conjugate leads to improved contrast between background and target.

Detailed Description Text (23):
Therapeutic drugs, administered alone or as targeted conjugates, are accompanied by similar disadvantages. Again, the goal is administration of the highest possible concentration of drug (to maximize exposure of target tissue), while remaining below the threshold of unacceptable normal organ toxicity (due to non-target tissue exposure). Unlike radioisotopes, however, therapeutic drugs need to be taken into a target cell to exert a cytotoxic effect. In the case of targeting moiety-therapeutic drug conjugates, it would be advantageous to combine the relative target specificity of a targeting moiety with a means for enhanced target cell internalization of the targeting moiety-drug conjugate.

Detailed Description Text (120):
1) increased tumor uptake in that more of the radioisotope will be targeted to the previously localized targeting moiety-streptavidin; and

Detailed Description Text (121):
2) increased tumor retention, if biotin is more stably bound to the radioisotope.

Detailed Description Text (264):
The use of this aspect of the present invention also facilitates the delivery of higher molecular weight therapeutic agent-bearing conjugates to target sites characterized by a three dimensional cellular array. For example, one or more ligand or anti-ligand molecules as well as a plurality of therapeutic agent molecules may be conjugated to a polymer to form an entity of the following formula:

Detailed Description Text (279):
Some polymers useful in the practice of this permeability enhancing aspect of the present invention serve solely as a carrier for multiple therapeutic agents. Preferred polymers also direct the biodistribution of the ligand or anti-ligand and therapeutic agents to which the polymer is bound to renal rather than, for example,

hepatobiliary excretion. For many administered therapeutic agents (e.g., radionuclides), renal excretion is preferred, especially for therapeutic protocols.

Detailed Description Text (487):
Both iodobiotin derivatives 2 exhibited .gtoreq.95% binding to immobilized avidin. Incubation of the products 2 with mouse serum resulted in no loss of the ability of 2 to bind to immobilized avidin. Biodistribution studies of a in male BALB/c mice showed rapid clearance from the blood (similar to .sup.186 Re-chelate-biotin conjugates described above). The radioiodobiotin 2 had decreased hepatobiliary excretion as compared to the .sup.186 Re-chelate-biotin conjugate; urinary excretion was increased as compared to the .sup.186 Re-chelate-biotin conjugate. Analysis of urinary metabolites of 2 indicated deiodination and cleavage of the biotin amide bond; the metabolites showed no binding to immobilized avidin. In contrast, metabolites of the .sup.186 Re-chelate-biotin conjugate appear to be excreted in urine as intact biotin conjugates. Intestinal uptake of 2 is <50% that of the .sup.186 Re-chelate-biotin conjugate. These biodistribution properties of 2 provided enhanced whole body clearance of radioisotope and indicate the advantageous use of 2 within pretargeting protocols.

Detailed Description Text (498):
A .sup.99m Tc-chelate-biotin conjugate is prepared as in Example II, above. The NR-LU-13-avidin conjugate is administered to a recipient and allowed to clear from the circulation. One of ordinary skill in the art of radioimmunoscintigraphy is readily able to determine the optimal time for NR-LU-13-avidin conjugate tumor localization and clearance from the circulation. At such time, the .sup.99m Tc-chelate-biotin conjugate is administered to the recipient. Because the .sup.99m Tc-chelate-biotin conjugate has a molecular weight of .apprxeq.1,000, crosslinking of NR-LU-13-avidin molecules on the surface of the tumor cells is dramatically reduced or eliminated. As a result, the .sup.99m Tc diagnostic agent is retained at the tumor cell surface for an extended period of time. Accordingly, detection of the diagnostic agent by imaging techniques is optimized; further, a lower dose of radioisotope provides an image comparable to that resulting from the typical three-step pretargeting protocol.

Detailed Description Text (692):
Mice bearing LS-180 colon tumor xenografts were injected with 200 micrograms NR-LU-10 antibody-streptavidin (MAb-StrAv) conjugate at time 0, which was allowed to prelocalize to tumor for 22 hours. At that time, 20 micrograms of AO-Bt was administered to one group of animals. Two hours later, 90 micrograms of a radioisotope-bearing, ligand-containing small molecule (PIP-biotin-dextran prepared as discussed in part B hereof) was administered to this group of mice and also to a group which had not received AO-Bt. The results of this experiment with respect to radiolabel uptake in tumor and clearance from the blood indicated that tumor-targeting of the radiolabeled biotin-containing conjugate was retained while blood clearance was enhanced, leading to an overall improvement in amount delivered to target/amount located in serum. The AUC tumor/AUC blood with clearing agent was 6.87, while AUC tumor/AUC blood without clearing agent was 4.45. Blood clearance of the circulating MAb-StrAv conjugate was enhanced with the use of clearing agent. The clearing agent was radiolabeled in a separate group of animals and found to bind directly to tumor at very low levels (1.7 pmol/g at a dose of 488 total pmoles (0.35 %ID/g), indicating that it does not significantly compromise the ability of tumor-bound MAb-StrAv to bind subsequently administered radiolabeled ligand.

Detailed Description Text (698):
Tumored mice injected with MAb-StrAv at time 0 as above; 50 micrograms of AO-Bt at time 22 hours; and 545 microcuries of I-131-PIP-biocytin at time 25 hours. Whole body radiation was measured and compared to that of animals that had not received clearing agent. 50 micrograms of AO-Bt was efficient in allowing the injected radioactivity to clear from the animals unimpeded by binding to circulating MAb-

StrAv conjugate. Tumor uptake of I-131-PIP-biocytin was preserved at the 50 microgram clearing agent dose, with AUC tumor/AUC blood of 30:1 which is approximately 15-fold better than the AUC tumor/AUC blood achieved in conventional antibody-radioisotope therapy using this model.

L15: Entry 40 of 87 File: USPT Sep 12, 2000

DOCUMENT-IDENTIFIER: US 6117977 A
** See image for Certificate of Correction **
TITLE: Type C lectins

Detailed Description Text (60):
Gene amplification and/or expression may be measured in a sample directly, for example, by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA [Thomas, Proc. Natl. Acad. Sci. USA 77, 5201-5205 (1980)], dot blotting (DNA analysis), or in situ hybridization, using an appropriately labeled probe, based on the sequences provided herein. Various labels may be employed, most commonly radioisotopes, particularly .sup.32 P. However, other techniques may also be employed, such as using biotin-modified nucleotides for introduction into a polynucleotide. The biotin then serves as a site for binding to avidin or antibodies, which may be labeled with a wide variety of labels,

Detailed Description Text (138):
Polymers are conjugated to oligosaccharide groups by oxidation using chemicals, e.g. metaperiodate, or enzymes, e.g. glucose or galactose oxidase, (either of which produces the aldehyde derivative of the carbohydrate), followed by reaction with hydrazide or amino derivatized polymers, in the same fashion as is described by Heitzmann et al., P.N.A.S., 71, 3537-41 (1974) or Bayer et al., Methods in Enzymology 62, 310 (1979), for the labeling of oligosaccharides with biotin or avidin. Further, other chemical or enzymatic methods which have been used heretofore to link oligosaccharides are particularly advantageous because, in general, there are fewer substitutions than amino acid sites for derivatization, and the oligosaccharide products thus will be more homogenous. The oligosaccharide substituents also are optionally modified by enzyme digestion to remove sugars, e.g. by neuraminidase digestion, prior to polymer derivatization.

Detailed Description Text (156):
For diagnostic applications, the antibodies of the invention typically will be labeled with a detectable moiety. The detectable moiety can be any one which is capable of producing, either directly or indirectly, a detectable signal. For example, the detectable moiety may be a radioisotope, such as .sup.3 H, .sup.14 C, .sup.32 P, .sup.35 S, or .sup.125 I, a fluorescent or chemiluminescent compound, such as fluorescein isothiocyanate, rhodamine, or luciferin; biotin; radioactive isotopic labels, such as, e.g., .sup.125 I, .sup.32 P, .sup.14 C, or .sup.3 H, or an enzyme, such as alkaline phosphatase, beta-galactosidase or horseradish peroxidase.

L15: Entry 44 of 87 File: USPT Oct 13, 1998

DOCUMENT-IDENTIFIER: US 5820879 A
TITLE: Method of delivering a lipid-coated condensed-phase microparticle composition

Detailed Description Text (90):
Other general classes of water-soluble compounds that are difficult to store in solution or on dehydration, such as free-radical initiators, dyes, and unstable water-soluble organic compounds are also contemplated.

Detailed Description Text (113):
After reaction of the sample fluid with the first reagent, migration of the sample along the strip leads to release of a second reagent, producing a second reaction that is diagnostic for the presence of the analyte or analyte-derived molecules. The second reagent may be, for example, a dye or other reporter reagent.

Detailed Description Text (114):
One advantages of the condensed-phase particle composition in this application is the stable storage of reagent compound, such as enzymes, antibodies, and dyes in a diagnostics kit. Another advantage is the rapid release of entrapped compound on contact with aqueous medium or by other activating means, such as introduction of monovalent counterions. This is in contrast to the relatively slow release of particles in crystallized or aggregated form.

Detailed Description Text (161):
Alternatively, the anti-ligand may be initially conjugated to a lipid component, such as a phospholipid, and this lipid then used in preparing lipid-encapsulated particles. The anti-ligand in this embodiment is contained on both sides of the lipid bilayers in the encapsulated particles.

Detailed Description Text (183):
Photoillumination can be used to generate ROS or acid and activate cleavage, when a lysogenic substance, such as a photoactivatable dye 144 is added to the encapsulated microparticle composition. Photoactivatable dyes known in the art include phenothiazinequinones (.lambda..sub.max, 650-850 nm), purpurins (690-780 nm), phthalocyanines (670-710 nm), sulfonated naphthalocyanines (730-780 nm), octaalkoxy phthalocyanines (660-780 nm), and clorins (740-770 nm). Such dyes, when exposed to an appropriate wavelength of light, produce reactive oxygen species, such as singlet oxygen, hydroxyl radical, hydrogen peroxide and superoxide radicals. These reactive oxygen species are also effective to cleave vinyl ether linkages. Alternatively, the lysogenic substance can be one that produces acid in response to photoillumination. Examples of such lysogens include 4-formyl-6-methoxy-3-nitrophenoxyacetic acid, triarylsulfonium salts, and dibenzenesulfonyldiazomethane derivatives.

Detailed Description Text (226):
Plasmalogen-containing encapsulated microparticle compositions can also be activated to release their contents by photoillumination, when the composition further includes a lysogenic substance that, in response to photoillumination at a pre-determined wavelength, produces ROS or acid. As discussed above, such compounds then stimulate lysis of the vesicular membrane and result in expulsion of

microparticle contents to the external medium. Lysogenic photo-sensitive compounds are well known in the art, and include but are not limited to photoactivatable dyes, such as phenothiazinequinones, purpurins, phthalocyanines, sulfonated naphthalocyanines, octaalkoxy phthalocyanines and clorins, and acid-producing light sensitive lysogens such as 4-formyl-6-methoxy-3-nitrophenoxyacetic acid, triarylsulfonium salts, and dibenzenesulfonyldiazomethane derivatives. Each of the foregoing compounds is stimulated by a known wavelength of light.

L15: Entry 67 of 87 File: USPT Jun 18, 1996

DOCUMENT-IDENTIFIER: US 5527528 A
TITLE: Solid-tumor treatment method

Brief Summary Text (29):
These liposomes have selected sizes in the size range 0.05 to 0.12 microns, and contain surface-bound anti-ligand molecules, an anti-tumor compound in liposome-entrapped form, and a surface coating of polyethylene glycol chains, at a surface concentration thereof sufficient to extend the blood circulation time of the liposomes severalfold over that of liposomes in the absence of such coating, thereby to localize the liposomes at the site of the solid tumor.

Drawing Description Text (2):
FIGS. 1A-1C are representations of antibody-liposome compositions, in which (a) an antibody molecule is directly attached to a liposome surface (FIG. 1A), (b) an antibody molecule is attached to a liposome surface by a polyethylene glycol (PEG) chain with a functionalized reactive end group (FIG. 1B), and (c) an antibody molecule is bound by biotin/avidin coupling to a liposome having surface-bound biotin moieties (FIG. 1C);

Drawing Description Text (6):
FIGS. 5A and 5B show the preparation of a biotinylated IgG (FIG. 5A), and binding of the biotinylated IgG molecule to a liposome surface containing biotinylated PE via high affinity interactions between surface-bound biotin, avidin, and biotin attached to IgG (FIG. 5B);

Detailed Description Text (18):
In another embodiment, illustrated in FIG. 1C, the antibody is a biotinylated antibody attached to the liposome outer surface by specific, high-affinity binding to avidin carried on the liposome outer surface. The avidin is bound noncovalently to the liposome outer surface by high-affinity interactions with biotin which has been used to derivatize lipid head groups on the liposome surface.

Detailed Description Text (19):
The figure shows a liposome bilayer portion 40 with a layer 42 of PEG chains, as above. The liposome outer surface contains a number of lipid polar head groups, such as lipid polar head group 44, which have been derivatized by biotin. To a biotin moiety on the liposome surface, such as biotin moiety 46, is bound an avidin molecule, such as avidin molecule 48. Each avidin molecule contains four high-affinity biotin binding sites, such as biotin binding site 50. To one or more of these sites is attached the liposome bound biotin as previously indicated. To one or more of the free-remaining sites can be bound a biotinylated antibody, such as biotinylated polypeptide 52, which is derivatized by a biotin molecule, such as biotin molecule 54.

Detailed Description Text (82):
In another method of treatment provided by the invention, an antibody modified by a ligand molecule, such as a biotinylated antibody, may be administered parenterally first. After about 24 to 48 hours to permit selective localization of the antibody to a target site, liposomes containing a liposome-entrapped compound, and a surface-bound anti-ligand molecule, such as avidin, are administered parenterally.

Liposomes with the surface-bound avidin will be retained at target sites by biotin molecules covalently attached to the antibodies.

Detailed Description Text (84):
These multivalent species serve to chase nonspecifically-bound biotinylated antibodies from sites in the bloodstream. After the chase, liposomes containing the therapeutic compound in liposome-entrapped form, the surface-bound anti-ligand molecules, such as avidin, and the PEG layer on the liposome surface are administered. Performing the chase with the multivalent species will prevent binding of liposomes containing liposome entrapped-drug at non-specific sites and will maximize the specificity of therapeutic compound targeting in vivo.

Detailed Description Text (85):
It will be appreciated that the present method can be employed for improved targeting of an imaging agent to a tumor, for tumor diagnosis. Here the imaging agent, typically a radioisotope in chelated form, or a paramagnetic molecule, is entrapped in liposomes, which are then administered IV to the subject being examined. After a selected period, typically 24-48 hours, the subject is then monitored, for example by gamma scintillation radiography in the case of the radioisotope, or by nuclear magnetic resonance (NMR) in the case of the paramagnetic agent, to detect regions of local uptake of the imaging agent.

L15: Entry 72 of 87 File: USPT Jan 9, 1996

DOCUMENT-IDENTIFIER: US 5482698 A
TITLE: Detection and therapy of lesions with biotin/avidin polymer conjugates

Brief Summary Text (77):
(b) injecting at least one dose of a clearing and localizing composition comprised of a polymer conjugated to more than one avidin molecule and permitting the conjugate to clear the biotin-protein conjugate from non-targeted sites and to bind to the biotin-protein conjugate accreted at the target lesion, wherein only one avidin of each multiavidin-polymer conjugate binds to a biotin receptor at the target lesion and thereby provides increased numbers of avidin receptors at the target lesion;

Detailed Description Text (13):
B--photoactivated dyes for detection or therapy;

Detailed Description Text (18):
The polymers most useful in the present invention are those which have a restricted stereochemistry. Such polymers allow for the adequate spacing of biotin (or avidin) moieties such that each biotin (or avidin) is capable of binding to an avidin (or biotin) moiety when its complimentary species is subsequently injected. Also, if the polymer conjugate is the subsequently injected composition and multiple biotin or avidin moieties are conjugated to the polymer, the position of the biotin or avidin residue and the relative rigidity of the polymer due to the restricted stereochemistry will be sufficient such that substantially only one of the multiple residue sites of the conjugate will be able to bind to a complimentary receptor site already present at the targeted lesion as a result of a previously injected composition. For example, biotin units substituted onto the polymer backbone will be unable to bind two avidin receptors present at the target lesion because (1) each biotin of the polymer conjugate will be more than 15 .ANG. from its neighbor and (2) the polymer will be sufficiently sterically rigid to not bend to enable two or more biotin units to bind with the corresponding number of avidin receptors. In this way, the fullest possible targeting amplification is achievable.

Detailed Description Text (124):
Suitable radioisotopes for the methods of the present invention include: Actinium-225, Astatine-211, Iodine-123, Iodine-125, Iodine-126, Iodine-131, Iodine-133, Bismuth-212, Bromine-77, Indium-111, Indium-113m, Gallium-67, Gallium-68, Ruthenium-95, Ruthenium-97, Ruthenium-103, Ruthenium-105, Mercury-107, Mercury-203, Rhenium-186, Rhenium-188, Tellurium-121m, Tellurium-122m, Tellurium-125m, Thulium-165, Thulium-167, Thulium-168, Technetium-99m, Fluorine-18, Silver-111,Platinum-197, Palladium-109, Copper-67, Phosphorus-32, Phosphorus-33, Yttrium-90, Scandium-47, Samarium-153, Lutetium-177, Rhodium-105, Praseodymium-142, Praseodymium-143, Terbium-161, Holmium-166, Gold-199, Cobalt-57, Cobalt-58, Chromium-51, Iron-59, Selenium-75, Thallium-201, and Ytterbium-169. Preferably the radioisotope will emit a particle or ray in the 10-7,000 kev range, more preferably 50-1,500 kev.

Detailed Description Text (129):
Among the therapeutic agents useful in the current invention are isotopes, drugs, toxins, fluorescent dyes activated by nonionizing radiation, hormones, hormone antagonists, receptor antagonists, enzymes or proenzymes activated by another

agent, autocrine or cytokine. Many drugs and toxins are known which have cytotoxic effects on cells. They are to be found in compendia of drugs and toxins, such as the Merck Index, Goodman and Gilman, and the like, and in the references cited above. Any such drug can be conjugated to or loaded onto the protein, polymer or biotin/avidin by conventional means well know in the art, and illustrated by analogy to those described above.

Detailed Description Text (130):
The present invention also contemplates dyes used, for example, in photodynamic therapy, conjugated to proteins, biotin or avidin and used in conjunction with appropriate nonionizing radiation.

Detailed Description Text (139):
The avidin or biotin may be conjugated to therapeutic agents such as drugs; toxins; agents useful in neutron capture therapy, such as boron and uranium; isotopes; fluorescent dyes activated by nonionizing radiation; hormones; autocrines; enzymes and proenzymes activated by another agent; cytokines; cytoprotective agents; etc., by methods known to those skilled in the art. U.S. Pat. No. 5,057,313, Shih et al, hereby incorporated by reference, teaches one such method.

Detailed Description Text (150):
Variations and modifications of these formulations will be readily apparent to the ordinary skilled artisan, as a function of the individual needs of the patient or treatment regimen, as well as of variations in the form in which the radioisotopes may be provided or may become available.

Detailed Description Text (155):
The scintigram is normally taken by a gamma imaging camera having one or more windows for detection of energies in the 50-500 keV range. Use of radioisotopes with higher energy, beta, or positron emissions would entail use of imaging cameras with the appropriate detectors, all of which are conventional in the art.

Detailed Description Text (158):
Magnetic resonance imaging (MRI) is effected in an analogous manner to scintigraphic imaging except that the imaging agents will contain magnetic resonance (mr) enhancing species rather than radioisotopes. It will be appreciated that the magnetic resonance phenomenon operates on a different principle from scintigraphy. Normally, the signal generated is correlated with the relaxation times of the magnetic moments of protons in the nuclei of the hydrogen atoms of water molecules in the region to be imaged. The magnetic resonance image enhancing agent acts by increasing the rate of relaxation, thereby increasing the contrast between water molecules in the region where the imaging agent accretes and water molecules elsewhere in the body. However, the effect of the agent is to decrease both T.sub.1 and T.sub.2, the former resulting in greater contrast while the latter results in lesser contrast. Accordingly, the phenomenon is concentration-dependent, and there is normally an optimum concentration of a paramagnetic species for maximum efficacy. This optimal concentration will vary with the particular agent used, the locus of imaging, the mode of imaging, i.e., spin-echo, saturation-recovery, inversion-recovery and/or various other strongly T.sub.1 -dependent or T.sub.2 -dependent imaging techniques, and the composition of the medium in which the agent is dissolved or suspended. These factors, and their relative importance are known in the art. See, e.g., Pykett, Scientific American, 246, 78(1982); Runge et al., Am. J. Radiol., 141, 1209(1983).

Detailed Description Text (190):
Polyaldehyde dextran (0.001 mmol) and avidin (0.03 mmol) are mixed together and stirred at 25.degree. C. for 16 hours at a pH of 7 in 40 mM PBS. Conjugation progress is followed by a suitable analytical procedure such as size-exclusion or HIC HPLC. The reaction mixture is treated with sodium borohydride (0.05 mmol) for 2 hours at room temperature at a pH of 8 in 40 mM PBS, to convert the imine groups to

amino groups and thus fix the avidin units to the dextran backbone. The (avidin).sub.n -dextran conjugates containing 2 and 3 avidin units per dextran are separated from each other and the rest of the reaction mixture by ion-exchange chromatography on S-sepharose equilibrated in 50 mM acetate buffer and run in a gradient of 0 to 2M sodium chloride. The biotin binding capability of the purified avidin conjugates is determined using the HABA test and a quantifiable amount of biotin conjugated to a fluorescent agent or radioisotope. The conjugates are further analyzed by polyacrylamide gel electrophoresis to verify the presence of 2 and 3 avidin units per dextran for the isolated products, respectively.

CLAIMS:

10. The method of claim 9 wherein the polymer has restricted stereochemistry such that each of the multiple biotin or avidin moieties conjugated to said polymer binds a complementary avidin or biotin moiety subsequently administered, and only one of the said multiple biotin or avidin moieties conjugated to said polymer binds to a complementary avidin or biotin moiety already present at the target site.

28. The method of claim 25, wherein the detection agent is one of a radionuclide, mri enhancing agent, photoactivated dye or differentiation agent.

35. The method of claim 34, wherein the therapeutic agent is one of an isotope, drug, toxin, fluorescent dye activated by nonionizing radiation, hormone, hormone antagonist, receptor antagonist, enzyme or proenzyme.

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L15: Entry 73 of 87 File: USPT May 30, 1995

DOCUMENT-IDENTIFIER: US 5420105 A
TITLE: Polymeric carriers for non-covalent drug conjugation

Brief Summary Text (5):
A large number of different classes of therapeutic agents have been considered, including beta-, gamma-, and alpha-emitting radioisotopes; plant and bacterial toxins; and a variety of antineoplastic drugs, including intercalating agents, antimetabolites, alkylating agents, and antibiotics. It is desirable to conjugate chemotherapeutic drugs to targeting molecules such as antibodies for the following reasons:

Detailed Description Text (80):
The present invention recognizes that this phenomenon (apparent loss of the targeting moiety-ligand from the target cell surface) may be used to advantage with regard to in vivo delivery of therapeutic agents generally, or to drug delivery in particular; provided that the loss is due to proper internalization of the conjugate. For instance, a targeting moiety may be covalently linked to both ligand and a polymeric carrier bearing therapeutic agents and administered to a recipient. Subsequent administration of anti-ligand crosslinks targeting moiety-ligand-polymer/therapeutic agent conjugates bound at the surface, inducing internalization of the conjugate (and thus the active agent). Alternatively, targeting moiety-ligand may be delivered to the target cell surface, followed by administration of anti-ligand-polymeric carrier-therapeutic agent(s).